

## 2016 Inflammatory Bowel Disease: Global view

# Endothelial dysfunction in inflammatory bowel diseases: Pathogenesis, assessment and implications

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**Author contributions:** Cibor D designed the paper, searched and analyzed literature, drafted and revised the paper, approved the final version; Domagala-Rodacka R and Rodacki T performed tables and figures, drafted and revised the paper, approved the final version; Jurchyszyn A, Mach T and Owczarek D searched and analyzed literature, drafted and the revised paper, approved the final version.

**Conflict-of-interest statement:** The authors do not declare any conflicts of interest.

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Received: April 29, 2015  
Peer-review started: May 12, 2015  
First decision: July 20, 2015

Revised: August 24, 2015

Accepted: November 30, 2015

Article in press: November 30, 2015

Published online: January 21, 2016

## Abstract

Endothelial dysfunction is considered one of the etiological factors of inflammatory bowel disease (IBD). An inflammatory process leads to functional and structural changes in the vascular endothelium. An increase of leukocyte adhesiveness and leukocyte diapedesis, as well as an increased vascular smooth muscle tone and procoagulant activity is observed. Structural changes of the vascular endothelium comprise as well capillary and venule remodeling and proliferation of endothelial cells. Hypoxia in the inflammatory area stimulates angiogenesis by up-regulation of vascular endothelial growth factor, fibroblast growth factor and tumor necrosis factor- $\alpha$ . Inflammatory mediators also alter the lymphatic vessel function and impair lymph flow, exacerbating tissue edema and accumulation of dead cells and bacteria. The endothelial dysfunction might be diagnosed by the use of two main methods: physical and biochemical. Physical methods are based on the assessment of large arteries vasodilatation in response to an increased flow and receptors stimulation. Flow-mediated vasodilatation (FMD) is the method that is the most widely used; however, it is less sensitive in detecting early changes of the endothelium function. Most of the studies demonstrated a decrease of FMD in IBD patients but no changes in the carotid intima-media thickness. Biochemical methods of detecting the endothelial dysfunction are based on the assessment of the synthesis of compounds produced both by the normal and damaged endothelium. The endothelial dysfunction is considered an initial step in the pathogenesis of atherosclerosis in the general

population. In IBD patients, the risk of cardiovascular diseases is controversial. Large, prospective studies are needed to establish the role of particular medications or dietary elements in the endothelial dysfunction as well to determine the real risk of cardiovascular diseases.

**Key words:** Biomarkers; Cytokines; Diagnosis; Endothelial dysfunction; Inflammatory bowel diseases; Inflammation; Microvasculature

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**Core tip:** Endothelial dysfunction seems to play an important role in the pathogenesis of inflammatory bowel disease (IBD). Inflammatory process leads to functional and structural changes in the vascular endothelium and in consequence its activation. It may contribute to cardiovascular complications, however, in IBD patients, the risk of cardiovascular disease is still controversial. Some of immunomodulatory medications used in IBD treatment may decrease the risk of endothelial dysfunction. In this review article, we present the role of the endothelium in the inflammatory process, diagnostic methods of its dysfunction and current knowledge of the cardiovascular disease risk in IBD.

Cibor D, Domagala-Rodacka R, Rodacki T, Jurczyszyn A, Mach T, Owczarek D. Endothelial dysfunction in inflammatory bowel diseases: Pathogenesis, assessment and implications. *World J Gastroenterol* 2016; 22(3): 1067-1077 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v22/i3/1067.htm> DOI: <http://dx.doi.org/10.3748/wjg.v22.i3.1067>

## INTRODUCTION

Inflammatory bowel disease (IBD) has a multifactorial etiology that has not been fully elucidated. Patients with IBD are genetically predisposed to pathological interactions between intestinal microflora and the immunological system<sup>[1]</sup>. Changes in the balance between regulatory and inflammatory cytokines lead to maintenance of the inflammatory process<sup>[2]</sup>. Dysfunction of the endothelium has also been considered an etiological factor.

The endothelium is a highly specialized, single-layered epithelium that lines internal surfaces of blood and lymph vessels and cardiac valves<sup>[3,4]</sup>. It plays a significant role in tissue flow, blood coagulation, regulation of substance transport across vascular walls, and regulation of the number and type of leukocytes migrating across vascular walls<sup>[3,5]</sup>. Endothelial cells are characterized by high metabolic activity, basement membrane-producing elements, intercellular components, and numerous substances that regulate blood vessel function, such as nitric oxide (NO), endothelin 1, prostacyclin 2, von Willebrand factor

(vWF), and cellular adhesion molecules (CAMs)<sup>[3,6]</sup> (Table 1). Under physiological conditions, the endothelium has dilating effect on vessels, prevents their excessive permeability, and prevents adhesion and aggregation of blood platelets and leukocytes. It also regulates fibrinolysis and the coagulation pathway<sup>[4,7]</sup> (Figures 1 and 2).

NO is a key mediator secreted by the endothelium and is produced from L-arginine by endothelial nitric oxide synthase (eNOS)<sup>[8]</sup>. It is released from the endothelium in response to shearing forces applied to the vascular wall<sup>[9]</sup>. It acts by increasing the concentration of cyclic guanosine monophosphate, which has a vasodilatory effect, and also inhibits the expression of cytokines, chemokines, and leukocyte adhesion substances, inhibits blood platelet adhesion and aggregation, and limits the proliferation of smooth muscle cells in the vascular wall<sup>[6,9]</sup>. Endothelium-derived hyperpolarizing factor also has a vasodilatory effect, whereas a vasoconstrictive effect is exhibited by endothelin 1 and endothelium-derived contracting factor.

## PATHOGENESIS

### Vascular endothelium

Endothelial dysfunction is “an imbalance between vasodilating and vasoconstricting substances produced by (or acting on) endothelial cells”<sup>[10]</sup>. Inflammation leads to functional and structural changes in vascular endothelium and its activation (Figure 3). These changes initially include increased leukocyte adhesiveness, leukocyte diapedesis, and vascular smooth muscle tone and procoagulant activity<sup>[5,11]</sup>. Activation of endothelial cells is promoted by the interactions between integrins and chemokine receptors with endothelial and mucosal ligands, the CAM superfamily, and chemokines<sup>[12,13]</sup>. Activated endothelium expresses CAMs and chemokines, which promote the recruitment of leukocytes<sup>[14,15]</sup>. Adhesion is the most important process determining which leukocytes migrate to tissues<sup>[16]</sup>. The three main classes of CAMs are selectins, integrins, and the immunoglobulin CAM superfamily, including intercellular adhesion molecule-1 (ICAM-1), ICAM-2, and vascular cell adhesion molecule-1 (VCAM-1)<sup>[17]</sup>. This process is mainly mediated by leukocyte CD11a/CD18 binding to ICAM-1 in the gut or by  $\alpha 4$ - $\beta 1$  or  $\alpha 4$ - $\beta 7$  binding to VCAM-1 and mucosal addressin cell adhesion molecule-1 (MAdCAM-1)<sup>[12]</sup>.

Cultures of human intestinal microvascular endothelial cells (HIMECs) have revealed unique leukocyte adhesion and growth patterns<sup>[18]</sup>. Significant changes, particularly an enhanced capacity to adhere to leukocytes, occur in chronically inflamed microvessels of patients with IBD compared to vessels from healthy controls and patients without IBD<sup>[5]</sup>. Microvascular expression of ICAM-1 and VCAM-1 is upregulated in patients with IBD<sup>[14,16]</sup>.

**Table 1** Factors released by endothelium

Factors regulating vascular tension		Factors regulating angiogenesis and cells proliferation		Factors regulating coagulation and fibrinolysis		Factors regulating inflammatory process	
Vasodilating effect	Vasoconstricting effect	Inhibition of proliferation	Stimulation of proliferation	Anticoagulant effect	Prothrombotic effect	Anti-inflammatory effect	Proinflammatory effect
Adrenomedullin (ADM)	Angiotensin II (AT II)	Extracellular proteases inhibitors	Adenosine (Ado)	Antithrombin III (AT III)	ET-1	NO	Adhesion molecules
Bradykinin (BK)	Endothelin-1 (ET-1)	NO	AT II	Heparan sulfate	PAF	PGI2	Chemokines
C-type natriuretic peptide (CNP)	Platelet-activating factor (PAF)	PGI2	ET-1	NO	Plasminogen activator inhibitor type 1 (PAI-1)		Cytokines
Endothelium-derived hyperpolarizing factor (EDHF)	Prostaglandin H2 (PGH2)	Transforming growth factor- $\beta$ (TGF- $\beta$ )	Heparan sulfate	PGI2	ROS		Nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B)
Nitric oxide (NO)	Thromboxane A2 (TXA2)		Insulin-like growth factor 1 (IGF-1)	Protein C (PC)	Tissue factor (TF)		
Prostacyclin (PGI2)	Reactive oxygen species (ROS)		Interleukins (IL)	Tissue factor pathway inhibitor (TFPI)	TXA2		
			ROS	Tissue-type plasminogen activator (t-PA)	Von Willebrand factor (VWF)		
			Vascular endothelial growth factor (VEGF)	Urokinase plasminogen activator (uPA)			

Increased MAdCAM-1 expression is also observed, which increases recruitment of  $\alpha 4$  integrin-expressing leukocytes<sup>[19]</sup>. Vowinkel *et al.*<sup>[20]</sup> demonstrated a significant increase in endothelial expression of CD40, resulting in increased recruitment of leukocytes.

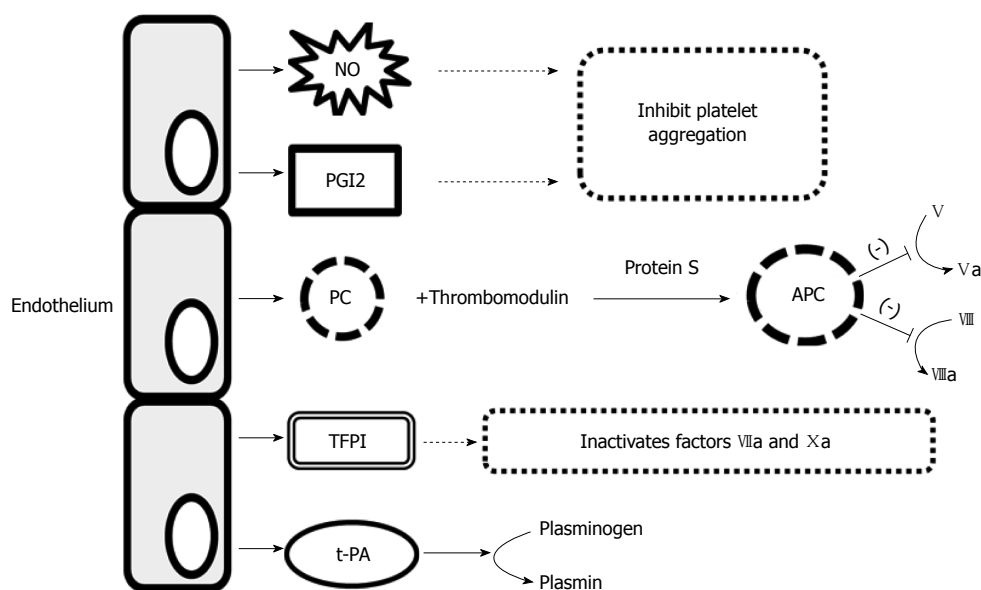
The risk for hyperhomocysteinemia is significantly higher in patients with IBD than in those without the disease<sup>[21,22]</sup>. HIMECs are activated by homocysteine alone or homocysteine combined with tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), leading to enhanced VCAM-1 expression, increased production of monocyte chemoattractant protein-1, and phosphorylation of p38 mitogen-activated protein kinase<sup>[16,23]</sup>.

Decreased NO production occurs in patients with IBD, which may be caused by increased arginase activity, an enzyme that competes with NOS, and a lack of inducible NOS mRNA expression<sup>[16,24,25]</sup>. Vascular endothelium is also a TNF- $\alpha$  target<sup>[11]</sup>. Binding of TNF- $\alpha$  to the TNF receptor leads to diminished eNOS protein expression and suppresses eNOS activity, which prevents degradation of asymmetric dimethylarginine (ADMA), an endogenous eNOS inhibitor<sup>[11,26]</sup>. Reactive oxygen species are produced in the inflamed area, which generate oxidative stress in vWF molecules. This process inhibits cleavage of vWF molecules by disintegrin and metalloproteinase with thrombospondin motif-13 and contributes to the creation of ultra-large vWF multimers leading to microvascular thrombosis in

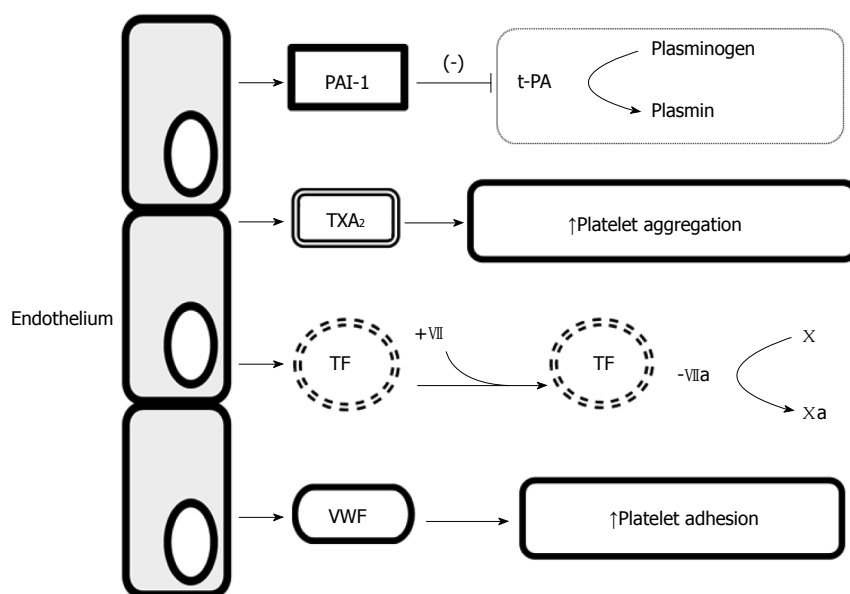
patients with IBD<sup>[13,17,27]</sup>.

Structural changes in vascular endothelium include capillary and venule remodeling and proliferation of endothelial cells<sup>[28]</sup>. Angiogenesis is a crucial process that sustains chronic inflammation in the gastrointestinal tract. Numerous inflammatory cell types, including macrophages, lymphocytes, mast cells, and fibroblasts, produce angiogenic factors and promote pathological angiogenesis in inflammatory tissues<sup>[16,29]</sup>. Hypoxia in the inflamed area stimulates angiogenesis by upregulating vascular endothelial growth factor (VEGF), fibroblast growth factor, and TNF- $\alpha$ <sup>[29]</sup>. Rutella *et al.*<sup>[30]</sup> suggested that inflamed HIMECs recruit platelets to produce higher levels of pro-angiogenic VEGF-A and CD40 ligand (CD40L) in patients with active ulcerative colitis (UC) and Crohn's disease (CD)<sup>[30]</sup>.

The CD40-CD40L pathway has a dual role, directly stimulating mucosal angiogenesis and activating CD40L-expressing T cells, which in turn stimulates intestinal fibroblasts to release angiogenic cytokines<sup>[31]</sup>. CD40 is upregulated by several cell types in patients with IBD, including antigen-presenting cells, monocytes, and endothelial cells. CD40L is overexpressed by T cells and platelets, and plasma CD40L levels are particularly high in patients with active IBD<sup>[31,32]</sup>. The CD40-CD40L pathway promotes mucosal inflammation and triggers increased production



**Figure 1 Anticoagulant activity of endothelium.** NO: Nitric oxide; PGI2: Prostacyclin; PC: Protein C; APC: Activated protein C; V, VIII: Coagulation factors; TFPI: Tissue factor pathway inhibitor; t-PA: Tissue-type plasminogen activator.



**Figure 2 Procoagulant activity of endothelium.** PAI-1: Plasminogen activator inhibitor type 1; t-PA: Tissue-type plasminogen activator; TXA2: Thromboxane A2; TF: Tissue factor; VWF: von Willebrand factor.

of various cytokines and cell adhesion molecules<sup>[31]</sup>. CD40 binding stimulates the production of TNF- $\alpha$ , and TNF- $\alpha$  increases CD40 expression<sup>[32]</sup>.

Intestinal endothelium is also involved in innate immunity by expressing toll-like receptors (TLRs), which increase the expression of proinflammatory genes and promote leukocyte chemotaxis, phagocytosis, and cytotoxicity as a second-line defense against bacterial entry<sup>[33]</sup>. Expression of TLRs on vascular endothelial cells is upregulated by vascular inflammation, as well as by lipopolysaccharide. Endothelial cells detect both extracellular and intracellular microbial invaders through TLRs and

activate the nucleotide oligomerization domain family of proteins<sup>[34]</sup>. Activated TLRs upregulate endothelial leukocyte adhesion molecules, increasing leukocyte transmigration<sup>[35]</sup>.

Tolstanova *et al.*<sup>[36]</sup> demonstrated that damage to endothelium and increased vascular permeability lead to hypoxia in four UC animal models, which increases the levels of oxygen-derived toxic free radicals and induces epithelial cell injury followed by the development of erosions and ulcerations. Genetic predisposition, activation of the VEGF gene, and activation of TLR2 by oxidation stress are responsible for increased endothelial microvascular permeability in

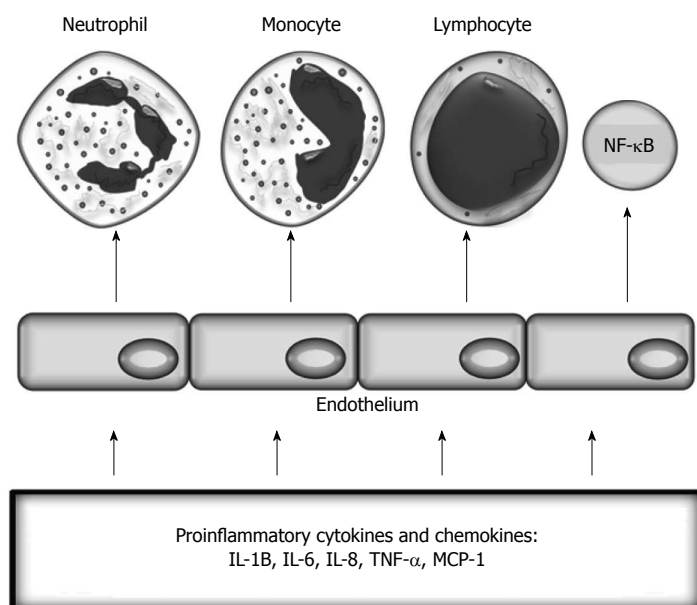


Figure 3 Inflammatory activation of endothelium. TNF: Tumour necrosis factor; IL: Interleukin.

patients with UC<sup>[36]</sup>.

### Lymphatic endothelium

The lymphatic vessels are responsible for intestinal lymphatic transport and elimination of accumulated fluid, inflammatory cells, and mediators. However, inflammatory mediators released alter lymphatic vessel function and impair lymph flow in patients with IBD, which exacerbates tissue edema and the accumulation of dead cells and bacteria. Lymphangiogenesis is mediated by binding of the lymphatic vascular endothelial selective growth factors VEGF-C and VEGF-D/VEGF receptor-3<sup>[37]</sup>.

Lymphatic obstruction, submucosal edema, and extended lymphangiogenesis are observed in patients with IBD<sup>[13,16]</sup>. Rahier *et al.*<sup>[38]</sup> reported that lymphatic density increases significantly in patients with CD and UC in both inflamed and non-inflamed intestinal mucosa. Tonelli *et al.*<sup>[39]</sup> demonstrated a correlation between parietal wall thickness and the severity of changes in lymphatic drainage in patients with IBD and stenosis, and reported that these abnormalities disappeared after strictureplasty. It remains unclear whether the impaired lymphatic function in patients with IBD is a consequence of inflammation or a preceding lymphangitis-like event<sup>[40]</sup>.

## DIAGNOSTIC METHODS OF DETECTING ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction is diagnosed using physical and biochemical methods. Physical methods are based on assessing vasodilation in large arteries in response to increased flow and receptor stimulation, mainly acetylcholine<sup>[3,34]</sup>. The most popular non-invasive procedures are presented in Table 2. Among

these methods, flow-mediated vasodilation (FMD) is the most widely used and the most sensitive<sup>[11,41]</sup>. However, these methods may not accurately reflect endothelial function in the microcirculation and are less sensitive for detecting early changes in endothelial function<sup>[11,42]</sup>.

The biochemical methods used to detect endothelial dysfunction are based on assessing the synthesis of compounds produced by normal and damaged endothelium. Numerous substances are released by abnormally activated endothelium (Table 2)<sup>[11,43]</sup>.

Endothelial activity in patients with IBD has been evaluated by physical and biochemical methods. Kocaman *et al.*<sup>[44]</sup> reported that both endothelial-dependent and endothelial-independent dilation are significantly worse in patients with severe or moderate UC than in controls, and that endothelial dysfunction is associated with activity-related extra-intestinal complications.

Roifman *et al.*<sup>[42]</sup> assessed endothelial dysfunction and found that 48 patients with UC and CD had lower pulse arterial tonometry values and shear stress reactive hyperemia compared to controls, which indicates endothelial dysfunction. However, no association was detected between clinical features such as disease duration, underlying therapy, or disease activity. Theocharidou *et al.*<sup>[45]</sup> reported that carotid intima-media thickness (cIMT) increases significantly in patients with UC and CD but lacks an association with clinical disease activity. Similarly, Aloï *et al.*<sup>[46]</sup> found an increase in cIMT and a decrease in FMD in pediatric patients. Zanolì *et al.*<sup>[47]</sup> demonstrated that arterial stiffness increases in patients with IBD independently of conventional cardiovascular risk factors and that carotid-radial pulse wave velocity (PWV) is positively correlated with disease duration. Arterial stiffness decreases following immunomodulatory therapy



**Table 2** Methods of endothelium dysfunction assessment

Proteins activated by normal and activated endothelium	Cell-based methods
Angiopoietin-1	Circulating angiogenic cells
Angiopoietin-2	Endothelial progenitor cells
Asymmetric dimethylarginine (ADMA)	Endothelial microparticles
Disintegrin and metalloproteinase with thrombospondin motif-13 (ADAMTS13)	
Intercellular adhesion molecule-1 (ICAM-1)	
Plasminogen-activator inhibitor (PAI-1)	
Selectins P and E	
Tissue plasminogen activator (t-PA)	
Thrombomodulin	
Vascular adhesion molecule-1 (VCAM-1)	
Vascular endothelial growth factor (VEGF)	
von Willebrand factor (vWF)	
Non-invasive physical methods	
Carotis intima-media thickness (cIMT)	
Flow mediated dilatation (FMD)	
Pulse arterial tonometry (PAT)	
Pulse wave analysis (PWA)	
Pulse wave velocity (PWV)	
Reactive hyperaemia index (RHI)	

(steroids and azathioprine or anti-TNF- $\alpha$ )<sup>[48]</sup>. Several studies have reported no differences in cIMT values in patients with IBD<sup>[49-52]</sup>. Ozturk *et al*<sup>[49]</sup> measured carotid femoral PWV, cIMT, and FMD in a group of patients with IBD without additional cardiovascular risks. They did not find any changes in cIMT, but they reported a significantly lower FMD and higher carotid femoral PWV. Similarly, a Korean study on 38 patients with IBD did not show an increase in cIMT compared to healthy controls. Disease severity was not correlated with cIMT but a positive correlation was detected with disease duration<sup>[50]</sup>. Kayahan *et al*<sup>[51]</sup> and Broide *et al*<sup>[52]</sup> reported no differences in cIMT, but the latter study reported a significantly impaired FMD in patients with IBD. Petr *et al*<sup>[53]</sup> evaluated the reactive hyperemia index (RHI) and E-selectin and ADMA levels in 21 patients with CD and reported a decrease in RHI but increases in E-selectin and ADMA levels.

A few studies have assessed the levels of endothelial dysfunction biomarkers in serum of patients with IBD and have provided controversial data. Some studies have reported an increase in VEGF level<sup>[54,55]</sup>. In another study, no difference in ICAM-1 or E-selectin expression was observed between patients with active UC and inactive CD<sup>[56]</sup>. In contrast, Adamska *et al*<sup>[57]</sup> reported a significant increase in E-selectin expression in patients with active CD compared to patients in remission. Similarly, Goggins *et al*<sup>[58]</sup> demonstrated an increase in levels of ICAM-1 and E-selectin in serum of patients with IBD but C-reactive protein (CRP) was a better indicator of disease activity. Another study found increased ICAM-1 levels in patients with IBD compared to healthy controls<sup>[55]</sup>. Magro *et al*<sup>[59]</sup> demonstrated that levels of P-selectin, E-selectin, VCAM, ICAM, VEGF, and angiogenin in serum are significantly lower in patients with inactive CD than in controls, suggesting dysfunction in the angiogenic process and wound repair. Lower levels of VEGF and angiogenin have been

demonstrated in patients with inactive IBD compared to those with active disease<sup>[60]</sup>.

## IMPLICATIONS

### Risk of cardiovascular complications

Chronic systemic inflammatory diseases are associated with accelerated atherosclerosis, a higher rate of cardiovascular disease (CVD), and increased morbidity and mortality compared to the general population<sup>[11,61-63]</sup>. Inflammatory mediators, such as CRP, TNF- $\alpha$ , interleukin (IL)-6, IL-18, and CD40L, are involved in the pathogenesis of inflammation and atherosclerosis<sup>[64,65]</sup>. Endothelial dysfunction is considered the initial step in the pathogenesis of atherosclerosis in the general population and may be a marker for future risk of cardiovascular events<sup>[66]</sup>.

The risk for CVD in patients with IBD is controversial. Some studies have demonstrated an increased risk for CVD in these patients<sup>[66-68]</sup>, whereas others have provided no evidence for an increased risk of mortality due to CVD<sup>[69-71]</sup>. Ruisi *et al*<sup>[72]</sup> found no increased risk for CVD in patients with IBD without traditional CVD risk factors after a 2-year follow-up. A meta-analysis performed by Fumery *et al*<sup>[73]</sup> and composed of 33 observational studies showed a higher risk for ischemic heart disease and arterial thromboembolism in patients with IBD but no increased risk for cardiovascular mortality. In addition, Singh *et al*<sup>[74]</sup> reported a 19% higher risk of CVD in patients with IBD and a modest increased risk for cardiovascular morbidity (from cerebrovascular accidents and ischemic heart disease), mostly in female patients<sup>[74]</sup>. Kristensen *et al*<sup>[75]</sup> performed a population-based study and demonstrated an increased risk for myocardial infarction in patients with IBD during flare-ups and during persistent disease activity, but not in patients in remission<sup>[76]</sup>.

Coronary flow reserve is impaired in patients with IBD, suggesting dysfunction in coronary microcirculation<sup>[76]</sup>.

Fan *et al.*<sup>[77]</sup> concluded that traditional risk factors, such as age, systolic blood pressure, body mass index, diabetes, and triglycerides, rather than inflammatory markers, are major predictors of arterial stiffness in patients with an inflammatory disease. In contrast, Ozturk *et al.*<sup>[49]</sup> suggested that patients with IBD without traditional cardiovascular risk factors have higher risks for endothelial dysfunction and atherosclerosis.

Some studies have suggested that patients with IBD, particularly those with CD, exhibit low levels of total cholesterol and low-density lipoprotein (LDL)<sup>[78]</sup>. However, Sappati Biyyani *et al.*<sup>[79]</sup> reported lower total cholesterol but higher LDL and lower high-density lipoprotein levels in patients with IBD in a large retrospective study. Changes in the lipid profile do not depend on disease activity<sup>[77]</sup>. Despite a lower incidence of traditional CVD risk factors in patients with IBD, these patients are diagnosed with coronary artery disease at a younger age<sup>[67,80]</sup>. It is important to emphasize that some patients with CD are tobacco smokers, which could also contribute to enhanced endothelial damage<sup>[81]</sup>. These findings indicate that large prospective studies are needed to determine the actual risks for CVD in patients with IBD.

### Pharmacological interventions and endothelial function

Pharmacological agents directed against TNF- $\alpha$ -mediated inflammation may decrease the risk for endothelial dysfunction and CVD in patients with IBD. Some studies that have addressed rheumatoid arthritis have demonstrated decreased levels of endothelial dysfunction biomarkers in plasma after anti-TNF- $\alpha$  therapy<sup>[11]</sup>. Other studies have shown improved endothelium-dependent vasodilation in patients with inflammatory diseases, including rheumatoid arthritis, spondyloarthritis, psoriasis, and IBD after initiating anti-TNF- $\alpha$  therapy<sup>[11,48,82]</sup>. However, whether this effect is permanent or transient remains controversial<sup>[11]</sup>. Arijis *et al.*<sup>[83]</sup> demonstrated that inflammatory cells from the intestinal lamina propria disappear after an infliximab infusion and that previously upregulated cell adhesion molecules are restored. Some authors have suggested that anti-TNF- $\alpha$  antibodies inhibit angiogenesis in patients with IBD<sup>[84,85]</sup>. Danese *et al.*<sup>[32]</sup> showed that anti-TNF- $\alpha$  downregulates the CD40/CD40L pathway.

The effects of TNF- $\alpha$  on the cardiovascular system could be both beneficial and harmful due to concentration-related differences in activation of different receptors<sup>[63,86]</sup>.

Data regarding corticosteroids are controversial as well. However, a systematic review of studies that assessed steroid administration in patients with rheumatoid arthritis did not report any effects of steroid use on endothelial function<sup>[87]</sup>.

At the same time, it is probable that methotrexate improves endothelial-dependent vasodilation in patients with rheumatoid arthritis<sup>[62]</sup>. A weekly low dose of methotrexate reduces disease-associated cardiovascular mortality. Thornton *et al.*<sup>[88]</sup> suggested that methotrexate induces cytoprotective genes by activating adenosine monophosphate protein kinase-cyclic AMP response element binding protein signaling, which prevents CVD.

*In vitro* studies have indicated that cyclosporine induces increased activation of endothelial cells<sup>[89]</sup>. However, some evidence suggests that cyclosporine A inhibits angiogenesis targeting VEGF-A<sup>[84,90]</sup>. At the same time, azathioprine and its metabolite, 6-mercaptopurine, may play a protective role against the activation of endothelial cells<sup>[91]</sup>.

New therapeutic options for patients with IBD include anti-adhesion molecules, such as vedolizumab, etrolizumab, and PF-00547659<sup>[92]</sup>. Vedolizumab targets  $\alpha 4$ - $\beta 7$  integrins and blocks interactions between  $\alpha 4$ - $\beta 7$  integrins and MAdCAM-1. Etrolizumab targets the  $\beta 7$  subunit, and PF-00547659 is a monoclonal antibody against MAdCAM-1<sup>[92]</sup>. Anti-chemokine receptor CCR 9 interferes with the activation of inflammatory cells in the intestine. Other medications, such as laquinimod and tofacitinib, reduce the synthesis of pro-inflammatory cytokines<sup>[92]</sup>.

As the lymphatic endothelium seems to play an adaptive role in the inflammation that occurs in patients with IBD, the inflammatory process may also be affected by stimulating lymphatic vessel functions, such as drainage and clearance of bacterial antigens, together with adaptive immunity<sup>[37]</sup>. D'Alessio *et al.*<sup>[37]</sup> demonstrated that adenoviral induction of the prolymphangiogenic factor VEGF-C in two different animal models significantly prevents the development of acute and chronic colitis, which supports the potential use of lymphangiogenic growth factors as a novel therapeutic approach<sup>[37]</sup>.

Improved endothelial function may also be achieved by increasing NO availability, as antioxidants affect the decrease in NO breakdown. Dietary components, such as vitamins C and E, have potential benefits on endothelial function and could prevent CVD<sup>[93]</sup>. Recent studies provide no evidence for a supportive role of vitamin D in endothelial function<sup>[94]</sup>. Ibrahim *et al.*<sup>[95]</sup> showed that treatment with long-chain n-3 polyunsaturated fatty acid decreases the expression of adhesion molecules in endothelial cells and has a potential anti-angiogenic role in animal models and *in vitro*.

## CONCLUSION

Endothelial dysfunction plays a pivotal role in the development of IBD. Some immunomodulatory medications used to treat IBD affect endothelial function; however, large studies on the interactions between the gut microvasculature, cytokines,

chemokines, cell adhesion molecules, inflammatory growth factors, and platelets are needed to create new therapeutic strategies for patients with IBD.

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